SUPPLEMENTARY DATA

Delphi-derived Framework for Healthspan-Oriented Care: The Cardiometabolic Health Perspective

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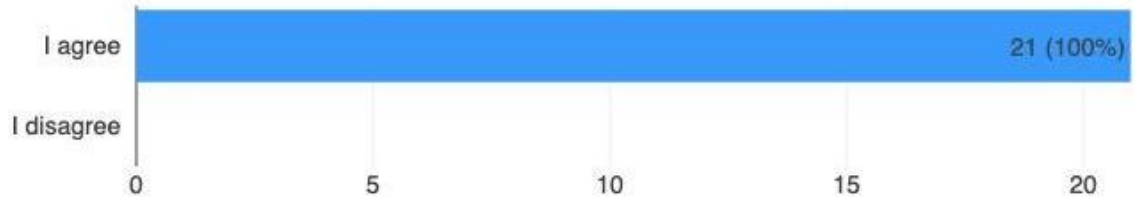
SUPPLEMENTARY DATA

Delphi Consensus Process: Panel Vote, Second Round

3. Biomarker-Based Healthy Longevity Diagnostics: From Routine Metrics to Biological Clocks

Statement: *The continued and routine use of both traditional CMD-related biomarkers (lipid profile, fasting glucose, HbA1c, hs-CRP, creatinine, liver enzymes), and select functional and imaging diagnostics, including ECG, Echocardiography, abdominal USG* ***is recommended*** *for cardiometabolic healthspan-oriented care both in individuals without or with well-controlled CMDs. These measures are well-established, widely accessible, and supported by strong clinical evidence forming the foundation of CMD risk assessment and management. Their integration into preventive and therapeutic care pathways enables effective risk stratification and monitoring of disease progression.*

Delphi Panel Vote



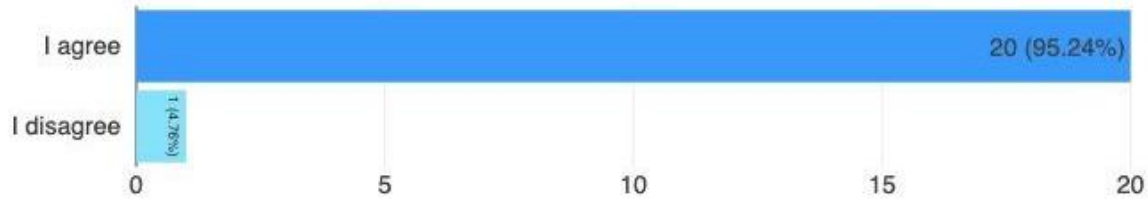
Statement: *The use of additional functional biomarkers, including Cardiopulmonary Exercise Testing (CPET), grip strength and frailty indices, as well as imaging modalities like DEXA scan and carotid intima-media thickness (CIMT)* ***should be considered in specific clinical contexts****, for cardiometabolic healthspan-oriented care both in individuals without or with well-controlled CMDs. These tools offer practical insights into systemic aging, musculoskeletal integrity, and subclinical atherosclerosis and are particularly valuable in geriatric and preventive cardiology for personalized risk profiling and early detection of functional decline.*

Delphi Panel Vote

Statement: *While growing evidence shows that epigenetic clocks, particularly GrimAge, are promising prognostic biomarkers for cardiometabolic diseases and mortality, their routine clinical use remains premature and* ***is not yet recommended*** *for cardiometabolic healthspan-oriented care both in individuals without or with well-controlled CMDs. Current data suggest that next-generation DNA methylation-based biomarkers (GrimAge, PhenoAge, and DunedinPACE) may provide greater predictive insight than traditional measures like telomere length or single-omics markers. As research progresses, the refinement and validation of multi-omics aging clocks could further improve risk assessment and personalization of care. For now, however, their main value lies in research and exploratory clinical applications until large-scale studies confirm their practical and actionable benefits.*

Delphi Panel Vote

SUPPLEMENTARY DATA



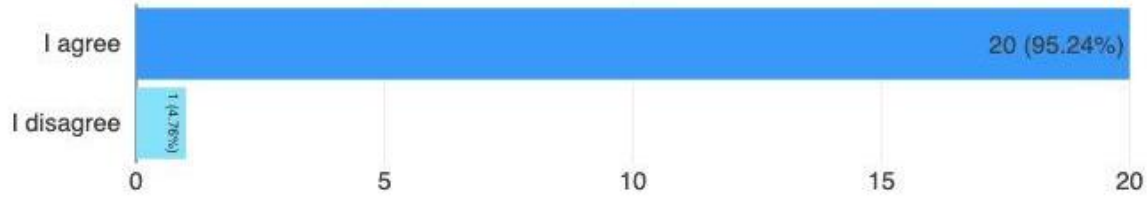
4. Healthy Longevity interventions in cardiometabolic health: from non-pharmacological to geroprotectors

4.1 Non-Pharmacological Approaches

4.1.1. Dietary Patterns

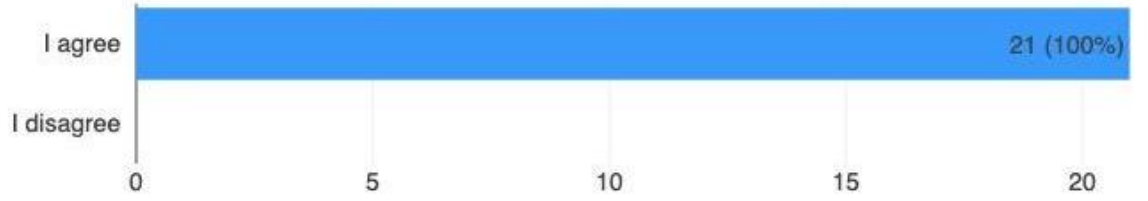
Statement: *The Mediterranean diet **is recommended** as a foundational dietary intervention for cardiometabolic healthspan-oriented care both in individuals without or with well-controlled CMDs. It consistently reduces cardiovascular mortality, improves metabolic markers, and supports healthy aging pathways. The Nordic diet and plant-based diets **should be considered** for cardiometabolic healthspan-oriented care both in individuals without or with well-controlled CMDs and are also supported in clinical contexts for reducing CMD risk and systemic inflammation, though their impact on aging biomarkers is less defined.*

Delphi Panel Vote



Statement: *In specific clinical settings, intermittent fasting and caloric restriction strategies **may be considered** for cardiometabolic healthspan-oriented care both in individuals without or with well-controlled CMDs**.** Intermittent fasting and caloric restriction strategies are under investigation and may show promise in modulating aging pathways including autophagy, insulin sensitivity, and effect on epigenetic aging clocks. However, these approaches should be individualized and monitored, as long-term adherence, metabolic effects, and impacts on aging remain under investigation. Their use may be most appropriate within structured programs and under clinical supervision due to an increased risk of frailty and sarcopenia in those over 65 y.o. As such, chronological age should be considered in the decision-making process.*

Delphi Panel Vote



SUPPLEMENTARY DATA

Statement: *The routine clinical use of personalized nutrition strategies based on genetic, microbiome, or metabolic profiling **is not yet recommended** for cardiometabolic healthspan-oriented care both in individuals without or with well-controlled CMDs. While these approaches have strong theoretical grounding and encouraging early data, they remain investigational due to the absence of validated algorithms, heterogeneous results, and lack of outcome-based evidence. **We support their continued evaluation within clinical research** settings to determine their future role in precision aging and nutrition care. Low-carbohydrate or ketogenic diets **are not yet recommended** for cardiometabolic healthspan-oriented care both in individuals without or with well-controlled CMDs and must be also restricted without according indication for long-term use.*

Delphi Panel Vote

4.1.2. Physical Activity

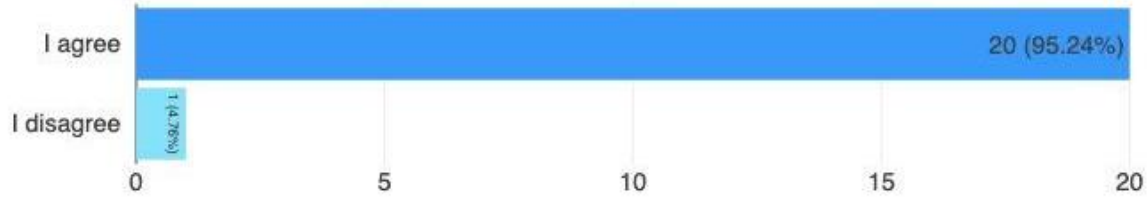
Statement: *Incorporation of regular physical activity including both aerobic and resistance exercise, **is recommended** as a standard component of cardiometabolic healthspan-oriented care, both in individuals without or with well-controlled CMDs, regardless of age. The following targets are advised i) aerobic activity: at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity exercise per week; (ii) resistance training: ≥2 sessions per week, engaging all major muscle groups. For adults aged 65 years and older, balance and flexibility exercises should be performed 2–3 times per week to support mobility, coordination, and fall prevention. Regular adherence to these recommendations helps preserve muscle mass and function, improves insulin sensitivity and cardiovascular fitness, and supports longevity through better metabolic and cognitive resilience.*

Delphi Panel Vote

4.1.3. Sleep Hygiene

Statement: *Assessment and improvement of sleep duration and quality including optimizing circadian alignment, ensuring ≥7 hours of restorative sleep, and addressing sleep disorders **is recommended** for cardiometabolic healthspan-oriented care both in individuals without or with well-controlled CMDs.*

Delphi Panel Vote

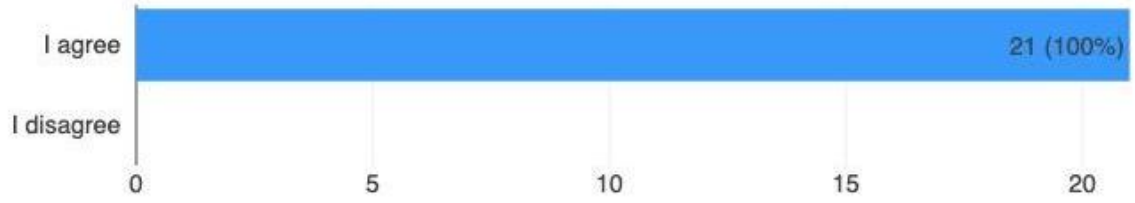


SUPPLEMENTARY DATA

1 **4.1.4. Stress Management**

Statement: *Evidence-based stress reduction strategies including mindfulness-based stress reduction, Heart Rate Variability (HRV)-guided biofeedback, and psychotherapy* ***should be considered*** *for cardiometabolic healthspan-oriented care both in individuals without or with well-controlled CMDs. These interventions may support autonomic balance, inflammation reduction, and aging modulation.*

Delphi Panel Vote



4.1.5. Weight Management

Statement: *Intentional weight loss of ≥10%* ***is recommended*** *for cardiometabolic healthspan-oriented care for patients with obesity or overweight, particularly in those with metabolic syndrome or T2DM. In parallel, efforts should focus on optimizing healthy body composition, with appropriate preservation of lean mass and reduction of excess fat mass, as both underweight and obesity are associated with increased cardiometabolic risk.*

Delphi Panel Vote

4.2. Pharmacological supplements and nutraceuticals

Statement: *Selective use of omega-3 fatty acids and vitamin D supplementation* ***should be considered*** *for cardiometabolic healthspan-oriented care in patients with well-controlled CMDs only when supported by evidence and patient-specific indications. Pharmaceutical formulations of icosapent ethyl and cholecalciferol are regulatory-approved agents with demonstrated benefits in defined clinical settings,when used within clinically accepted dose ranges, including patients with hypertriglyceridemia or vitamin D deficiency. Non-standardized nutraceutical formulations of omega-3 and vitamin D should therefore be used cautiously, as variability in content and bioavailability limits reproducibility of outcomes. Their clinical use of non-standardized nutraceutical formulations is limited by the existing evidence and should remain adjunctive to evidence-based lifestyle and pharmacologic therapies.*

Delphi Panel Vote

SUPPLEMENTARY DATA

Statement: *Magnesium, DHEA, creatine, and folate/B12, as well as various experimental compounds, lack robust clinical validation and standardized dosing guidelines. Polyphenols such as resveratrol and curcumin demonstrate promising anti-inflammatory and antioxidant effects in preclinical and small clinical studies; however, large, well-controlled trials are needed to establish their clinical relevance. Thus those compounds* ***are not yet recommended*** *for cardiometabolic healthspan-oriented care both in individuals without or with well-controlled CMDs. Until more conclusive data become available, their use should be limited to research settings. Evidence-based lifestyle interventions and proven medical therapies remain the foundation of cardiometabolic healthspan-oriented care.*

Delphi Panel Vote

Statement: *The routine clinical use of multivitamins* ***is not recommended*** *for cardiometabolic healthspan-oriented care both in individuals without or with well-controlled CMDs without strong evidence of efficacy and safety: Multivitamin supplements lack robust clinical validation and show signs of harm.*

Delphi Panel Vote

4.3 Pharmacological Geroprotectors

Statement: *Selective, evidence-based use of pharmacological agents with geroprotective effects may be considered within their approved clinical indications: hormonal replacement therapy (HRT), when appropriately prescribed in women within 10 years of menopause onset,* ***may be considered*** *as a* ***geroprotective agent*** *both for patients without or with well-controlled CMDs. Similarly, metformin, SGLT2 inhibitors, and GLP-1/GIP receptor agonists, according to their clinically approved use,* ***may be considered*** *as* ***geroprotectors*** *in patients with well-controlled CMDs, recognizing their possible indirect effects on aging pathways.*

Delphi Panel Vote

SUPPLEMENTARY DATA

Statement: *The routine clinical use of pharmacological agents as geroprotectors* ***is not yet recommended*** *for cardiometabolic healthspan-oriented care in individuals without concrete indications: Although agents such as metformin, SGLT2 inhibitors, and GLP-1 receptor agonists demonstrate clear benefits for managing specific cardiometabolic conditions like T2DM, obesity, chronic kidney disease (excluding metformin) or heart failure, their off-label use purely for aging delay lacks regulatory approval and definitive evidence. These drugs should be reserved for their approved indications while research continues to clarify their geroprotective potential in healthy individuals.*

Delphi Panel Vote

Statement: *The use of rapalogs, senolytics, and other novel geroprotectors* ***is not yet recommended*** *for cardiometabolic healthspan-oriented care in individuals without or with well-controlled CMDs without clear FDA and EMA approval in particular fields. These emerging agents should remain within the domain of controlled clinical trials and experimental research. While promising in preclinical models—demonstrating lifespan extension and improved healthspan—they currently lack sufficient human safety and efficacy data. Until rigorous evidence from randomized controlled trials becomes available, their use outside of research protocols is premature and not advised.*

Delphi Panel Vote

SUPPLEMENTARY DATA

Supplementary Table 1. Summary of available diagnostic interventions for Cardiometabolic Healthspan-Oriented Care

Biomarker Type	Description / Key Metrics	Clinical Utility	Class and Evidence Level	Justification	Level of Current Use	Ref
3.1. Routine diagnostics						
3.1 Traditional Biomarkers	Lipids, glucose, HbA1c, hs-CRP, creatinine, liver enzymes	Foundation of CMD risk stratification and therapy monitoring	Class I, Level A	Multiple large RCTs and meta-analyses (e.g., statin and diabetes outcome trials), long prospective cohorts, and guideline endorsements demonstrate prognostic and therapeutic utility across populations; cornerstone tests for risk stratification and treatment decisions	Fully integrated into routine care. Age-related disease diagnostics and surveillance	[1-8]
3.1.2 Imaging & Instrumental Diagnostics	ECG, EchoCG, DEXA, CIMT, US, PFTs, Coronary Artery Calcium (CAC) scoring	Detect CMD and aging physiology (e.g., sarcopenia, steatosis). Risk prediction (strong); Risk reclassification (moderate–strong)	Class I (Routine) / IIa (Selective), Level A	Large prospective studies and randomized/registry data (e.g., MESA for CAC), plus meta-analyses and guideline inclusion (ACC/AHA, ESC) support diagnostic, prognostic and risk-reclassification value; widely validated in clinical practice	Standard or selectively used diagnostics. Fully integrated into routine care. Age-related disease diagnostics and surveillance	[1,2]
2 3.2. Clinical Biomarker and Functional & Physiological Clocks						
3.2.1. Clinical Biomarker Clocks	Phenotypic Age, Biological Age (Levine model)	Integrate routine lab data for aging and CMD risk.	Class IIc, Level B	Derivation and validation are based on large observational cohorts and computational modelling, but no robust interventional RCTs demonstrate outcome modification or routine clinical benefit	Research use; commercial availability; not standardized clinically	[9, 10]
3.2.2. Functional & Physiological Clocks	VO_2max age, PWV, grip strength, leg press strength, frailty index	Reflect musculoskeletal, vascular, and fitness age	Class IIa, Level B	Strong prospective associations with morbidity/mortality and RCTs showing that interventions (exercise, rehab) improve the measures; intervention RCTs exist for components (VO_2max, sarcopenia), but meta-analytic trial evidence specifically for "age-clock" use is limited.	Used in geriatrics and preventive cardiology	[11]
3.2.3. Multi-Omics & Composite Clocks	AI-based clocks, digital biomarkers	Integrate omics and sensor data; personalized aging trajectories	Class IIc, Level C	Early-stage, technology-driven models validated primarily in observational cohorts and pilot studies; no large RCTs or outcome trials yet to confirm clinical utility.	Tech-driven longevity clinics, wellness platforms	[12]
3.3. Aging Clocks						

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3.3.1 Epigenetic Clocks	GrimAge, PhenoAge, DunedinPACE	Estimate biological age; predict CMD, mortality, response to interventions.	Class IIc, Level B	Robust prognostic evidence from multiple cohort studies showing prediction of mortality and CVD (especially GrimAge/PhenoAge); a small number of interventional trials (e.g., CALERIE for DunedinPACE) suggest clock modulation but RCT evidence for clinical outcomes and replication across large trials is limited	Research use; commercial availability; not standardized clinically for routine diagnosis or treatment decisions.	[13, 14]
3.3.2 Transcriptomic Clocks	RNAAge, ImmuneAge	Assess gene expression patterns tied to immune aging	Class IIc, Level B	Promising observational/transcriptomic studies show associations with immune/biologic age, but evidence is early and lacks RCT/interventional validation.	Research only	[15]
3.3.3 Proteomic Clocks	GDF15, PAI-1, PRO-Age	Reflect inflammation, senescence, metabolic aging	Class IIc, Level B	Large proteomic cohort analyses demonstrate mortality prediction, yet evidence remains observational with no RCTs showing outcome modification	Research use; commercial availability; not standardized clinically	[16]
3.3.4 Metabolomic & Lipidomic Clocks	MetaboAge, Lipidomic panels	Capture cardiometabolic health, atherosclerotic burden	Class IIc, Level B	Strong cohort evidence (e.g., UK Biobank metabolomics analyses) linking metabolomic signatures to multimorbidity and mortality; however, interventional or RCT data demonstrating clinical benefit are lacking	Research use; commercial availability; not standardized clinically	[17, 18]
3.3.5 Glycan Clocks	GlycanAge	Track immune aging, inflammation, hormonal changes, T2D and CVD risk	Class IIc, Level B	Analytical and observational studies document associations with inflammation, immune aging and disease risk, but no RCTs demonstrate outcome improvement or clinical utility.	Research use; commercial availability; not standardized clinically	[19]
3.4. Other approaches						
3.4.1 Telomere Length Analysis	Telomere shortening as aging proxy	CMD, cancer, mortality associations; low individual risk precision	Class IIc, Level B	Large meta-analyses (>700k sample confirm population-level associations with age and some disease risks, but individual predictive precision is low and no interventional RCTs show that telomere-targeted changes translate to clinical benefit	Research use; lacks clinical harmonization	[20]

SUPPLEMENTARY DATA

Supplementary Table 2. Dietary Patterns in Cardiometabolic Healthspan-Oriented Care

Dietary Pattern	Class and Evidence Level	Justification	Strengths	Limitations / Risks	Guideline Reference(s)	Recommendation
Mediterranean Diet	Class I, Level A	Multiple RCTs (e.g., PREDIMED), meta-analyses show reduced mortality, CV events, and improved metabolic markers; robust evidence.	Strong evidence for reduced all-cause and CV mortality, improved metabolic profile, anti-inflammatory and epigenetic benefits	Non-significant; broad applicability	ESC/EAS 2019 Dyslipidemia Guidelines [21]; ESC/EASD 2023 Diabetes Guidelines [22, 23]	Foundational recommendation for all individuals
Nordic Diet	Class IIa, Level A	Systematic review/meta-analysis of RCTs [24] confirms benefits; slightly less adoption, but meets Level A threshold.	Similar benefits to the Mediterranean diet; favourable for lipid control and inflammation	Fewer long-term studies; limited adoption outside Northern Europe	Endorsed in EASO/ESC Obesity Guidelines (2023) as a culturally adapted alternative	Useful alternative where culturally feasible
Plant-Based / Vegan Diets	Class IIa, Level A	Meta-analyses [25, 26] and interventional trials [27] support reduced mortality, improved risk markers.	Reduces CMD incidence, inflammation, and body weight; may support healthy aging pathways	Risk of nutritional deficiencies (B12, iron, omega-3) if unbalanced	ESC/EASD 2023 Diabetes Guidelines [22, 23]; EASO/EFAD Obesity Guidelines 2023 [28].	Recommended in selected individuals with monitoring
Low-Carbohydrate / Ketogenic Diets	Class IIc, Level A	Meta-analyses of RCTs [29], [30–32] show efficacy for weight loss and metabolic health; long-term safety uncertain, but meets Level A.	Effective short-term for weight loss and glycemic control	Long-term CV safety uncertain; potential adverse lipid changes; adherence difficult	EASO/EFAD/ESC Obesity Guidelines 2023 (conditional use) [28]	Not recommended for long-term use; only specific indications
Intermittent Fasting / Caloric Restriction	Class IIb, Level A	Multiple RCTs (CALERIE, [33], [27, 34–36] and meta-analyses confirm metabolic benefits and aging-clock modulation.	Improves insulin sensitivity, autophagy, and may slow epigenetic clocks (PhenoAge, DunedinPACE)	Limited long-term human data; adherence variable; possible risks in the frail elderly.	Not yet included in ESC/EAS/ESH guidelines; addressed in scientific statements (AHA 2021; EASO 2023 position papers)	Promising but investigational; consider under supervision, high risk of frailty and sarcopenia
Personalized Nutrition (genetic/ microbiome-based)	Class IIc, Level C	Only early trials (e.g., PREDICT pilot); no large RCTs or meta-analyses; remains experimental.	Strong theoretical rationale; early trials (e.g., PREDICT) suggest improved glycemic response	Lack of standardized algorithms; not outcome-validated	Not included in ESC/EAS/EASD guidelines; discussed in emerging precision medicine position papers	Research use only; not recommended for routine practice

SUPPLEMENTARY DATA

Supplementary Table 3. Other Non-Pharmacological Interventions in Cardiometabolic Healthspan-Oriented Care

Intervention Type	Description & Mechanism	Clinical Utility	Class and Evidence Level	Justification	Direct Evidence	Indirect Evidence	Level of Current Use
Physical Activity	Regular aerobic and resistance exercise improves cardiovascular, metabolic, and muscular health; supports telomere stability and mitochondrial function.	Reduces CMD risk, cancer, mortality; improves VO_2max, glucose tolerance, lipid profiles.	Class I, Level A	Large meta-analysis of prospective studies [37]) and many RCTs show mortality/CV risk reduction and improved VO_2max, fitness, and biomarkers [38].	Prospective studies: high activity linked to HR 0.62 (95% CI 0.58–0.67) for mortality [37].	Epigenetic clocks studies show slower DNAm aging with higher activity [38])	Fully integrated into CMD and aging guidelines.
Sleep Hygiene	Adequate sleep duration and circadian alignment optimize endocrine and metabolic regulation. Regular, sufficient sleep improves autonomic balance, glucose/insulin dynamics, BP dipping, and inflammatory tone—all core pathways in vascular and metabolic aging. (Summarized in AHA scientific statements/guidelines (1).)	Reduces obesity, insulin resistance, depression; improves mitochondrial repair.	Class I, Level B	Evidence is primarily observational [39-41]; no large RCTs prove mortality or aging outcomes.	Poor sleep linked to accelerated CMDs [39]	Poor sleep linked to accelerated GrimAgeAccel, DunedinPACE [40–42]	Widely endorsed by sleep medicine guidelines.
Stress Management	Mindfulness, breathwork, HRV biofeedback lower cortisol, sympathetic tone; reduce inflammation.	Improves BP, HRV, glycemic control, systemic inflammation.	Class IIa, Level B	Multiple small-to-medium RCTs show physiological improvements; small studies link resilience to slower epigenetic aging [43].	Mixed results. No effect on MACE, but evidence in reduction of mortality [44].	Epigenetic studies link resilience to slower aging [43].	Common in integrative care, underused in primary CMD care [45, 46].

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Weight Management	Sustained weight loss ≥5–10% reduces visceral fat, CMD risk. Reducing weight modifies multiple risk pathways simultaneously and, with GLP-1/GIP agonists and surgery, now has hard-outcome signals (MACE ↓ with semaglutide; mortality/CV events ↓ after surgery).	Improves BP, insulin sensitivity, and lipid profile.	Class I, Level A	Meta-analyses of RCTs confirm mortality benefit; interventions reduce epigenetic aging [47].	Meta-analyses confirm mortality benefit [48] [49, 50].	DNAm age reduction with weight loss in obesity. [47]	Standard care in CMD and T2DM [51].

Supplementary Table 4. Pharmaceutical supplements and nutraceuticals for Cardiometabolic Healthspan-Oriented Care

Supplement	Description & Mechanism	Clinical Utility	Class and Evidence Level	Justification	Direct Evidence	Indirect Evidence	Level of Current Use
Omega-3 Fatty Acids esters	Anti-inflammatory, anti-thrombotic; stabilizes membranes.	Strong CV prevention; slows aging markers.	Class IIa Level A	Large RCTs (VITAL) and multiple meta-analyses support CV benefit/prevention endpoints and aging-marker studies; meets "multiple RCTs / meta-analysis" threshold. [52, 53]	VITAL RCT: MI HR 0.72 (95% CI 0.59–0.90). [52]	DNAm age reduction (PhenoAge, GrimAge2).[53]	Recommended in the treatment of hypertriglyceridemia.
Magnesium	Cofactor in >300 enzymes; regulates glucose, DNA repair.	Supports BP, glucose regulation, inflammation control.	Class IIc, Level B	Evidence is observational (NHANES association with PhenoAgeAccel), No RCTs with aging outcomes available; [54].	No RCTs.	NHANES: higher intake linked to ↓ PhenoAgeAccel [54]	Commonly used, underrecognized in aging care.
Polyphenols	Resveratrol, curcumin, EGCG mimic CR; antioxidant, anti-inflammatory.	Potential anti-aging; mitochondrial support.	Class IIc, Level B	There are randomized trials showing effects on methylation/aging markers (e.g., DIRECT-PLUS RCT) but not multiple independent	Mechanistic support; observational data.	DIRECT-PLUS RCT: ↓ Li mAge, Hannum mAge. [55]	Widely marketed, not standardized.

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				RCTs/meta-analyses [55].			
Vitamin D	Hormone modulating immunity, Ca balance.	Supports bone health, CMD prevention modestly.	Class IIa, Level A	Numerous RCTs and meta-analyses for CV / clinical endpoints and large trials summarized in the supplement, so meets Level A for the existence of multiple RCT/meta-analytic data (though aging-biomarker benefit is limited) [53, 56].	No significant MACE reduction [56]. A trend to reduce all-cause mortality and association with decreased incidence of falls ≥ 75 years [57].	Indirect evidence exists in vitamin D deficiency and with omega-3 supplementation [53] and in Vitamin D deficiency [58]. No indirect epigenetic aging effect.	Standard in vitamin D deficiency
Creatine	Supports ATP recycling, muscle, cognition.	Benefits sarcopenia, cognition.	Class IIc, Level B	RCT evidence exists for benefits on muscle/sarcopenia and functional outcomes; observational mortality signals noted, but not multiple RCT/meta-analyses specifically for longevity/ epigenetic evidence is emerging [59].	NHANES: Inverse association with all-cause mortality (B = -0.094; P = 0.04) [59].	correlated with lower GrimAge mortality predictors ($r \approx -0.04$, $p < 0.05$) [60].	Growing longevity commercial use [61].
Multivitamins	Broad micronutrient supplement.	No proven longevity benefit; possible aging acceleration.	Class III, Level A	Multiple randomized trials and meta-analytic/epidemiologic analyses exist with mixed or null/harms signals (the supplement notes observational ↑ mortality and RCT evidence of accelerated aging markers) — qualifies as Level A (multiple RCTs/meta-analyses).	Observational: ↑ mortality risk (HR 1.04); RCT: accelerated aging markers [62].	Mixed epidemiologic data.	Widespread OTC, not recommended for longevity.
Folic Acid & B12	Methyl donors, DNA repair.	Prevents deficiency, supports cognition.	Class IIc, Level A	A meta-analysis of 21 randomized clinical trials for stroke prevention — this is Level A	Meta-analysis: ~10% ↓ stroke risk[63].	No DNAm benefit [64].	Routine in geriatrics.

				(meta-analysis of RCTs). [63, 64].			
DHEAs	Endogenous adrenal steroid; precursor to sex hormones.	Proposed anti-aging and anabolic effects; limited proven benefit.	Class IIc, Level C	Pilot trials and observational studies [65].	No significant MACE reduction	A pilot study (N=10) showed DNAm age reduction (Horvath p = 0.0009, GrimAge p = 0.0049) as part of the TRIIM combination. Causality cannot be attributed to DHEA alone [65, 66].	Widely available as an over-the-counter supplement; occasional off-label use in age-related fatigue or endocrine decline

Supplementary Table 5. Geroprotective Pharmacological Interventions

Compound/ Class	**Mechanism**	**Clinical Utility**	**Class and Evidence Level**	**Justification**	**Direct Evidence**	**Indirect Evidence**	**Level of Current Use**
Metformin	AMPK activation, CR mimetic.	CV, cancer protection; anti-aging candidate.	Class IIb, Level A	Multiple RCTs & meta-analyses show mortality reduction in diabetes and preliminary epigenetic aging benefit [67, 68].	Observational : HR 0.72 for mortality in T2DM [67]	Small RCT shows slower Horvath, Hannum EAA [68]	Approved for T2DM, off-label in PCOS.
Rapalogs	mTOR inhibition, autophagy.	Promising anti-aging.	Class IIc, Level C	No large RCTs in aging outcomes yet. Phase 2–3 immune function RCTs in older adults[69] show mechanistic benefits. Clinical aging outcome trials remain ongoing	No RCTs results.	Strong animal evidence. Limited epigenetic data.	Research only.

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GLP-1 RAs	Incretin, insulin sensitization, and weight loss.	CV risk reduction, obesity care.	Class IIb, Level A	Large CV outcome RCTs (**LEADER, SUSTAIN**) demonstrate reduced MACE; RCT shows slowed epigenetic aging, evidence strong for cardiometaboli c protection [70].	LEADER, SUSTAIN: HR 0.74 for MACE. [70]	Epigenetic benefit in HIV trial [70].	Approved for T2DM/obesit y (Class I, Level A).
SGLT2 Inhibitors	Glycosuria, CV/renal protection.	Mortality reduction in CVD, HF.	Class IIb, Level A	Multiple RCTs (EMPA-REG, DAPA-HF, etc.) [72-73] demonstrate robust reductions in CV and renal outcomes; No aging biomarker data yet, but outcome evidence	EMPA-REG: CV death HR 0.62. [72-73]	No aging biomarkers yet.	Approved in T2DM, HF, CKD; (Class I, Level A).
Senolytics	Clear senescent cells.	Aging-focused trials are ongoing.	Class IIc, Level C	Current evidence is limited to small pilot/open-label trials (e.g., **D+Q in diabetic kidney disease**) showing biomarker changes, not outcomes. No large RCTs	No human RCTs yet.	Strong preclinical support.	Experimental [74, 75].
NAD+ Boosters	Mitochondrial support.	Popular, unproven in humans.	Class IIc, Level B	Small RCTs (e.g., NR trial in cognitive impairment), but no large trials/meta-analyses [76].	Neutral RCT findings. [76]	Preclinical benefit.	Widely sold, unregulated.
Acarbose	Delays carbohydrate absorption.	Prevents T2DM progression .	Class IIb, Level B	The **STOP-NIDDM RCT** showed reduced diabetes incidence;	STOP-NIDDM: HR 0.75 for diabetes conversion. [77]	Observationa l anti-aging signals.	Approved for T2DM.

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				observational data suggest anti-aging signals. Limited to single landmark RCT with aging relevance [77].			
Bisphosphonates	Inhibit osteoclast activity; bone protection.	Mortality benefits post-fracture; anti-aging signals.	Class IIb, Level B	RCTs in osteoporosis showed evidence for mortality reduction in post-fracture patients; aging benefit observational.	Zoledronic acid ↓ mortality by ~28% post-hip fracture [69, 78].	No DNAm data.	Approved for osteoporosis [79]
Aspirin	Irreversible COX-1 inhibition; antiplatelet, anti-inflammatory.	Secondary CV prevention; harmful in primary prevention ≥70 y.	Class III, Level A	Multiple large RCTs and meta-analyses (e.g., **ASPREE, McNeil et al. 2018**) demonstrate mortality harm in primary prevention but clear benefit in secondary prevention [80]. Colon studies show epigenetic slowing.	ASPREE: ↑ all-cause mortality (HR 1.14) in ≥70 y; secondary prevention benefit established [80].	Colon data: slows cancer-related epigenetic aging [81].	Routine for secondary prevention only.
Beta-blockers	β-adrenergic blockade; ↓ HR, BP, arrhythmias.	Mortality benefit in HFrEF; uncertain in preserved EF.	Class IIb, Level A	Multiple RCTs (e.g., **MERIT-HF**) and meta-analyses confirm mortality reduction in HFrEF; no aging biomarker data. Robust outcome evidence in selective populations	MERIT-HF: HR 0.66 for mortality in HFrEF [71].	No DNAm data.	Standard in HFrEF, post-MI; not for primary prevention .[82]
Hormone Replacement Therapy (HRT)	Restores estrogen/testosterone; symptom relief. Treat bothersome menopausal symptoms and prevent osteoporotic fractures—key to healthy aging and functional preservation.	Safe in early post-menopause; lowers MACE in 50–59-year-olds.	Class IIb, Level A (sex-specific)	Multiple large RCTs (WHI, follow-ups) show reduced MACE and no increase in mortality in the early post-menopausal period, providing a strong evidence base. Strong sex-specific evidence base, though not directly linked to aging biomarkers	WHI: ↓ MACE, no ↑ mortality with early CEE±MPA use [83], [83, 84].	No DNAm-clock data.	Approved for menopausal symptoms; individualized risk–benefit [85- 88].

SUPPLEMENTARY DATA

References

[1] McEvoy JW, McCarthy CP, Bruno RM, Brouwers S, Canavan MD, Ceconi C, et al. (2024). 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. Eur Heart J, 45:3912–4018.

[2] Jones DW, Ferdinand KC, et al. (2025). 2025 AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Hypertension, 82:e212–e316.

[3] Mach F, Koskinas KC, Roeters van Lennep JE, Tokgözoğlu L, Badimon L, Baigent C, et al. (2025). 2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J, 46:4359–4378.

[4] Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. (2019). 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary. J Am Coll Cardiol, 73:3168–3209.

[5] Marx N, Federici M, Schütt K, Müller-Wieland D, Ajjan RA, Antunes MJ, et al. (2023). 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. Eur Heart J, 44:4043–4140.

[6] American Diabetes Association Professional Practice Committee (2025). 10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes-2025. Diabetes Care, 48:S207–S238.

[7] McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. (2023). 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J, 44:3627–3639.

[8] Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. (2022). 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol, 79:e263–e421.

[9] Fong S, Pabis K, Latumalea D, Dugersuren N, Unfried M, Tolwinski N, et al. (2024). Principal component-based clinical aging clocks identify signatures of healthy aging and targets for clinical intervention. Nat Aging, 4:1137–1152.

[10] Nwanaji-Enwerem JC, Mair WB (2022). Redefining Age-Based Screening and Diagnostic Guidelines: An Opportunity for Biological Aging Clocks in Clinical Medicine? Lancet Healthy Longev, 3:e376–e377.

[11] Moqri M, Herzog C, Poganik JR, Biomarkers of Aging Consortium, Justice J, Belsky DW, et al. (2023). Biomarkers of aging for the identification and evaluation of longevity interventions. Cell, 186:3758–3775.

[12] Lu JK, Wang W, Mahadzir MDA, Poganik JR, Moqri M, Herzog C, et al. (2025). Digital biomarkers of ageing for monitoring physiological systems in community-dwelling adults. Lancet Healthy Longev, 6:100725.

[13] Fuentealba M, Rouch L, Guyonnet S, Lemaitre J-M, de Souto Barreto P, Vellas B, et al. (2025). A blood-based epigenetic clock for intrinsic capacity predicts mortality and is associated with clinical, immunological and lifestyle factors. Nat Aging, 5:1207–1216.

[14] Teschendorff AE, Horvath S (2025). Epigenetic ageing clocks: statistical methods and emerging computational challenges. Nat Rev Genet, 26:350–368.

[15] Zakar-Polyák E, Csordas A, Pálovics R, Kerepesi C (2024). Profiling the transcriptomic age of single-cells in humans. Commun Biol, 7:1397.

[16] Argentieri MA, Xiao S, Bennett D, Winchester L, Nevado-Holgado AJ, Ghose U, et al. (2024). Proteomic aging clock predicts mortality and risk of common age-related diseases in diverse populations. Nat Med, 30:2450–2460.

[17] Zhang S, Wang Z, Wang Y, Zhu Y, Zhou Q, Jian X, et al. (2024). A metabolomic profile of biological aging in 250,341 individuals from the UK Biobank. Nature Communications, 15:1–19.

[18] Huang H, Chen Y, Xu W, Cao L, Qian K, Bischof E, et al. (2025). Decoding aging clocks: New insights from metabolomics. Cell Metab, 37:34–58.

[19] Rapčan B, Song M, Frkatović-Hodžić A, Pribić T, Vuk J, Beletić A, et al. (2024). Glycan clock of ageing-analytical precision and time-dependent inter- and i-individual variability. Geroscience, 46:5781–5796.

[20] Ye Q, Apsley AT, Etzel L, Hastings WJ, Kozlosky JT, Walker C, et al. (2023). Telomere length and chronological age across the human lifespan: A systematic review and meta-analysis of 414 study samples including 743,019 individuals. Ageing Res Rev, 90:102031.

[21] Mach F, Koskinas KC, Roeters van Lennep JE, Tokgözoğlu L, Badimon L, Baigent C, et al. (2025). 2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias. Atherosclerosis, 409:120479.

[22] Marx N, Federici M, Schütt K, Müller-Wieland D, Ajjan RA, Antunes MJ, et al. (2023). 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. Eur Heart J, 44:4043–4140.

[23] American Diabetes Association Professional Practice Committee (2025). Summary of Revisions: Standards of Care in Diabetes-2025. Diabetes Care, 48:S6–S13.

SUPPLEMENTARY DATA

[24] Massara P, Zurbau A, Glenn AJ, Chiavaroli L, Khan TA, Viguiliouk E, et al. (2022). Nordic dietary patterns and cardiometabolic outcomes: a systematic review and meta-analysis of prospective cohort studies and randomised controlled trials. Diabetologia, 65:2011–2031.

[25] Tan J, Zhang S, Jiang Y, Li J, Yang C (2024). Plant-based diet and risk of all-cause mortality: a systematic review and meta-analysis. Front Nutr, 11:1481363.

[26] Kraus WE, Bhapkar M, Huffman KM, Pieper CF, Krupa Das S, Redman LM, et al. (2019). 2 years of calorie restriction and cardiometabolic risk (CALERIE): exploratory outcomes of a multicentre, phase 2, randomised controlled trial. Lancet Diabetes Endocrinol, 7:673–683.

[27] Dwaraka VB, Aronica L, Carreras-Gallo N, Robinson JL, Hennings T, Carter MM, et al. (2024). Unveiling the epigenetic impact of vegan vs. omnivorous diets on aging: insights from the Twins Nutrition Study (TwiNS). BMC Med, 22:301.

[28] Busetto L, Dicker D, Frühbeck G, et al. (2024). A new framework for the diagnosis, staging and management of obesity in adults. Nat Med, 30:2395–2399.

[29] Silverii GA, Cosentino C, Santagiuliana F, Rotella F, Benvenuti F, Mannucci E, et al. (2022). Effectiveness of low-carbohydrate diets for long-term weight loss in obese individuals: A meta-analysis of randomized controlled trials. Diabetes Obes Metab, 24:1458–1468.

[30] Izquierdo AG, Lorenzo PM, Costa-Fraga N, Primo-Martin D, Rodriguez-Carnero G, Nicoletti CF, et al. (2025). Epigenetic Aging Acceleration in Obesity Is Slowed Down by Nutritional Ketosis Following Very Low-Calorie Ketogenic Diet (VLCKD): A New Perspective to Reverse Biological Age. Nutrients, 17:1060.

[31] Patikorn C, Saidoung P, Pham T, Phisalprapa P, Lee YY, Varady KA, et al. (2023). Effects of ketogenic diet on health outcomes: an umbrella review of meta-analyses of randomized clinical trials. BMC Med, 21:196.

[32] Cioffi I, Evangelista A, Ponzo V, Ciccone G, Soldati L, Santarpia L, et al. (2018). Intermittent versus continuous energy restriction on weight loss and cardiometabolic outcomes: a systematic review and meta-analysis of randomized controlled trials. J Transl Med, 16:371.

[33] Wang B, Wang C, Li H (2025). The impact of intermittent fasting on body composition and cardiometabolic outcomes in overweight and obese adults: a systematic review and meta-analysis of randomized controlled trials. Nutr J, 24:120.

[34] Waziry R, Ryan CP, Corcoran DL, Huffman KM, Kobor MS, Kothari M, et al. (2023). Effect of long-term caloric restriction on DNA methylation measures of biological aging in healthy adults from the CALERIE trial. Nat Aging, 3:248–257.

[35] Kwon D, Belsky DW (2021). A toolkit for quantification of biological age from blood chemistry and organ function test data: BioAge. Geroscience, 43:2795–2808.

[36] Ramaker ME, Corcoran DL, Apsley AT, Kobor MS, Kraus VB, Kraus WE, et al. (2022). Epigenome-wide Association Study Analysis of Calorie Restriction in Humans, CALERIETM Trial Analysis. J Gerontol A Biol Sci Med Sci, 77:2395–2401.

[37] Tarp J, Dalene KE, Fagerland MW, Steene-Johannesen J, Hansen BH, Anderssen SA, et al. (2024). Physical Activity Volume, Intensity, and Mortality: Harmonized Meta-Analysis of Prospective Cohort Studies. Am J Prev Med, 67:887–896.

[38] You Y, Chen Y, Ding H, Liu Q, Wang R, Xu K, et al. (2025). Relationship between physical activity and DNA methylation-predicted epigenetic clocks. NPJ Aging, 11:27.

[39] Merikanto I, Lahti T, Puolijoki H, Vanhala M, Peltonen M, Laatikainen T, et al. (2013). Associations of chronotype and sleep with cardiovascular diseases and type 2 diabetes. Chronobiol Int, 30:470–477.

[40] Diao T, Liu K, Zhou L, Wang Q, Lyu J, Zhu Z, et al. (2025). Sleep patterns and DNA methylation age acceleration in middle-aged and older Chinese adults. Clinical Epigenetics, 17:1–8.

[41] Carskadon MA, Chappell KR, Barker DH, Hart AC, Dwyer K, Gredvig-Ardito C, et al. (2019). A pilot prospective study of sleep patterns and DNA methylation-characterized epigenetic aging in young adults. BMC Research Notes, 12:1–5.

[42] Lee H-S, Kim B, Park T (2024). The association between sleep quality and accelerated epigenetic aging with metabolic syndrome in Korean adults. Clin Epigenetics, 16:92.

[43] Zhang A, Zhang Y, Meng Y, Ji Q, Ye M, Zhou L, et al. (2024). Associations between psychological resilience and epigenetic clocks in the health and retirement study. Geroscience, 46:961–968.

[44] Schmidt KES, Waclawovsky G, dos Santos AM, de Quadros AS, Schmidt MM (2024). Effect of a nonpharmacological psychological stress management intervention on major cardiovascular events and mortality in patients with coronary artery disease: A systematic review and meta-analysis of randomized clinical trials. Int J Stress Manag, 31:219–237.

[45] Levine GN, Cohen BE, Commodore-Mensah Y, Fleury J, Huffman JC, Khalid U, et al. (2021). Psychological health, well-being, and the mind-heart-body connection: A scientific statement from the American Heart Association. Circulation, 143:e763–e783.

SUPPLEMENTARY DATA

[46] Wu Z, Qu J, Zhang W, Liu G-H (2024). Stress, epigenetics, and aging: Unraveling the intricate crosstalk. Mol Cell, 84:34–54.

[47] Petersen CL, Christensen BC, Batsis JA (2021). Weight management intervention identifies association of decreased DNA methylation age with improved functional age measures in older adults with obesity. Clin Epigenetics, 13:46.

[48] Rubino F, Cummings DE, Eckel RH, Cohen RV, Wilding JPH, Brown WA, et al. (2025). Definition and diagnostic criteria of clinical obesity. Lancet Diabetes Endocrinol, 13:221–262.

[49] Ma C, Avenell A, Bolland M, Hudson J, Stewart F, Robertson C, et al. (2017). Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and cancer: systematic review and meta-analysis. BMJ, 359:j4849.

[50] Kritchevsky SB, Beavers KM, Miller ME, Shea MK, Houston DK, Kitzman DW, et al. (2015). Intentional weight loss and all-cause mortality: a meta-analysis of randomized clinical trials. PLoS One, 10:e0121993.

[51] American Diabetes Association Professional Practice Committee (2025). 8. Obesity and weight management for the prevention and treatment of type 2 diabetes: Standards of care in diabetes-2025. Diabetes Care, 48:S167–S180.

[52] Khan SU, Lone AN, Khan MS, Virani SS, Blumenthal RS, Nasir K, et al. (2021). Effect of omega-3 fatty acids on cardiovascular outcomes: A systematic review and meta-analysis. EClinicalMedicine, 38:100997.

[53] Bischoff-Ferrari HA, Gängler S, Wieczorek M, Belsky DW, Ryan J, Kressig RW, et al. (2025). Individual and additive effects of vitamin D, omega-3 and exercise on DNA methylation clocks of biological aging in older adults from the DO-HEALTH trial. Nat Aging, 5:376–385.

[54] Ma J, Li P, Jiang Y, Yang X, Luo Y, Tao L, et al. (2024). The association between dietary nutrient intake and acceleration of aging: Evidence from NHANES. Nutrients, 16:1635.

[55] Yaskolka Meir A, Keller M, Hoffmann A, Rinott E, Tsaban G, Kaplan A, et al. (2023). The effect of polyphenols on DNA methylation-assessed biological age attenuation: the DIRECT PLUS randomized controlled trial. BMC Med, 21:364.

[56] Mirza AMW, Almansouri NE, Muslim MF, Basheer T, Uppalapati SV, Lakra S, et al. (2024). Effect of vitamin D supplementation on cardiovascular outcomes: an updated meta-analysis of RCTs. Ann Med Surg (Lond), 86:6665–6672.

[57] Shah VP, Nayfeh T, Alsawaf Y, Saadi S, Farah M, Zhu Y, et al. (2024). A Systematic Review Supporting the Endocrine Society Clinical Practice Guidelines on Vitamin D. J Clin Endocrinol Metab, 109:1961–1974.

[58] Vetter VM, Sommerer Y, Kalies CH, Spira D, Bertram L, Demuth I (2022). Vitamin D supplementation is associated with slower epigenetic aging. Geroscience, 44:1847–1859.

[59] Ostojic SM (2025). Dietary creatine intake and all-cause mortality among U.S. adults: a linked mortality analysis from the NHANES study. Appl Physiol Nutr Metab, 50:1–6.

[60] Ostojic SM, Kavecan I (2025). Linking dietary creatine to DNA methylation-based predictors of mortality in individuals aged 50 and above. Lifestyle Genom, 1–8.

[61] Dos Santos EEP, de Araújo RC, Candow DG, Forbes SC, Guijo JA, de Almeida Santana CC, et al. (2021). Efficacy of Creatine Supplementation Combined with Resistance Training on Muscle Strength and Muscle Mass in Older Females: A Systematic Review and Meta-Analysis. Nutrients, 13:3757.

[62] Loftfield E, O'Connell CP, Abnet CC, Graubard BI, Liao LM, Beane Freeman LE, et al. (2024). Multivitamin Use and Mortality Risk in 3 Prospective US Cohorts. JAMA Netw Open, 7:e2418729.

[63] Zhang N, Zhou Z, Chi X, Fan F, Li S, Song Y, et al. (2024). Folic acid supplementation for stroke prevention: A systematic review and meta-analysis of 21 randomized clinical trials worldwide. Clin Nutr, 43:1706–1716.

[64] Sae-Lee C, Corsi S, Barrow TM, Kuhnle GGC, Bollati V, Mathers JC, et al. (2018). Dietary Intervention Modifies DNA Methylation Age Assessed by the Epigenetic Clock. Mol Nutr Food Res, 62:e1800092.

[65] Schooling CM, Zhao JV (2025). Dehydroepiandrosterone sulfate on lifespan in men and women using Mendelian randomization. Nutr Metab Cardiovasc Dis, 35:104128.

[66] Fahy GM, Brooke RT, Watson JP, Good Z, Vasanawala SS, Maecker H, et al. (2019). Reversal of epigenetic aging and immunosenescent trends in humans. Aging Cell, 18:e13028.

[67] Campbell JM, Bellman SM, Stephenson MD, Lisy K (2017). Metformin reduces all-cause mortality and diseases of ageing independent of its effect on diabetes control: A systematic review and meta-analysis. Ageing Res Rev, 40:31–44.

[68] Li M, Bao L, Zhu P, Wang S (2022). Effect of metformin on the epigenetic age of peripheral blood in patients with diabetes mellitus. Frontiers in Genetics, 13:955835.

[69] Mannick JB, Teo G, Bernardo P, Quinn D, Russell K, Klickstein L, et al. (2021). Targeting the biology of ageing with mTOR inhibitors to improve immune function in older adults: phase 2b and phase 3 randomised trials. Lancet Healthy Longev, 2:e250–e262.

SUPPLEMENTARY DATA

[70] Corley MJ, Dwaraka V, Pang APS, Labbato D, Smith R, Eckard AR, et al. (2025). Semaglutide Slows Epigenetic Aging in People with HIV-associated lipohypertrophy: Evidence from a Randomized Controlled Trial. medRxiv, 2025.07.09.25331038.

[71] Herlitz J, Wikstrand J, Denny M, Fenster P, Heywood T, Masszi G, et al. (2002). Effects of metoprolol CR/XL on mortality and hospitalizations in patients with heart failure and history of hypertension. J Card Fail, 8:8–14.

[72] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. (2015). Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med, 373:2117–2128.

[73] McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. (2019). Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med, 381:1995–2008.

[74] Hickson LJ, Langhi Prata LGP, Bobart SA, Evans TK, Giorgadze N, Hashmi SK, et al. (2019). Senolytics decrease senescent cells in humans: Preliminary report from a clinical trial of Dasatinib plus Quercetin in individuals with diabetic kidney disease. EBioMedicine, 47:446–456.

[75] Atlante S, Gottardi Zamperla M, Cis L, Farsetti A, Gaetano C (2025). Senolytic therapies for cardiovascular aging: tackling fibrosis and metabolic dysfunction. Eur J Intern Med, 140:106413.

[76] Orr ME, Kotkowski E, Ramirez P, Bair-Kelps D, Liu Q, Brenner C, et al. (2024). A randomized placebo-controlled trial of nicotinamide riboside in older adults with mild cognitive impairment. Geroscience, 46:665–682.

[77] Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, et al. (2002). Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. Lancet, 359:2072–2077.

[78] Lyles KW, Colón-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al. (2007). Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med, 357:1799–1809.

[79] Samakkarnthai P, Saul D, Zhang L, Aversa Z, Doolittle ML, Sfeir JG, et al. (2023). and effects of zoledronic acid on senescence and senescence-associated secretory phenotype markers. Aging (Albany NY), 15:3331–3355.

[80] McNeil JJ, Nelson MR, Woods RL, Lockery JE, Wolfe R, Reid CM, et al. (2018). Effect of Aspirin on All-Cause Mortality in the Healthy Elderly. N Engl J Med, 379:1519–1528.

[81] Noreen F, Chaber-Ciopinska A, Regula J, Schär P, Truninger K (2020). Longitudinal analysis of healthy colon establishes aspirin as a suppressor of cancer-related epigenetic aging. Clin Epigenetics, 12:164.

[82] Rossello X, Prescott EIB, Kristensen AMD, Latini R, Fuster V, Fagerland MW, et al. (2025). β blockers after myocardial infarction with mildly reduced ejection fraction: an individual patient data meta-analysis of randomised controlled trials. Lancet, 406:1128–1137.

[83] Roehm E (2015). A Reappraisal of Women's Health Initiative Estrogen-Alone Trial: Long-Term Outcomes in Women 50-59 Years of Age. Obstet Gynecol Int, 2015:713295.

[84] Manson JE, Aragaki AK, Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, et al. (2017). Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials. JAMA, 318:927–938.

[85] Cho L, Kaunitz AM, Faubion SS, Hayes SN, Lau ES, Pristera N, et al. (2023). Rethinking Menopausal Hormone Therapy: For Whom, What, When, and How Long? Circulation, 147:597–610.

[86] "The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel (2022). The 2022 hormone therapy position statement of The North American Menopause Society. Menopause, 29:767–794.

[87] Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, et al. (2003). Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA, 290:1729–1738.

[88] Liu Y, Li C (2024). Hormone Therapy and Biological Aging in Postmenopausal Women. JAMA Netw Open, 7:e2430839.

SUPPLEMENTARY DATA